

Asthma in Adults



Anil Nanda, MD^{a,b,c,*}, Anita N. Wasan, MD^d

KEYWORDS

• Asthma • Adult • Allergy • Cough • Rhinitis • Sinusitis • COPD • ACO

KEY POINTS

- The diagnosis of asthma is a clinical one, but objective measures, such as pulmonary function testing, can be used to aid in the diagnosis.
- There are multiple associated comorbidities with asthma, including rhinitis, sinusitis, gastroesophageal reflux disease, obstructive sleep apnea, and depression.
- Pharmacologic therapies include inhaled corticosteroids (ICS), ICS–long-acting β -agonist combinations, leukotriene antagonists, long-acting muscarinic antagonists, and short-acting β -agonists. The latest therapies are biologic medications for severe asthma.
- Special populations include pregnant adults with asthma, patients with exercise-induced asthma/bronchoconstriction, older adults with asthma, and patients with occupational asthma.
- Individualized and precision therapy for each patient is essential.

INTRODUCTION

Asthma affects approximately 300 million people worldwide and approximately 7.5% of adults in the United States.^{1,2} Among adults, asthma results in about 10.5 million physician office visits per year and affects approximately 8.7% of blacks, 7.6% of whites, and 5.8% of Hispanics.² Asthma is characterized by inflammation of airways, variable airflow obstruction, and bronchial hyperresponsiveness.³ It is a heterogeneous condition that is diagnosed clinically.² A detailed history and physical examination are essential, but objective measures, such as pulmonary function testing (PFT), methacholine challenge, and fractional exhaled nitric oxide (FeNO), can aid in the diagnosis. Comorbidities of asthma include rhinitis, sinusitis, gastroesophageal reflux disease (GERD), obstructive sleep apnea (OSA), and depression.³ It is vital to understand that asthma can initially occur at any age, even in older adults. Adult-onset asthma is often misdiagnosed as chronic obstructive pulmonary disease (COPD).

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^a Asthma and Allergy Center, 724 West Main Street, Suite 160, Lewisville, TX 75067, USA;

^b Asthma and Allergy Center, 4900 Long Prairie Road, Suite 100, Flower Mound, TX, USA;

^c Division of Allergy and Immunology, University of Texas Southwestern Medical Center, Dallas, TX, USA; ^d Allergy and Asthma Center, 6824 Elm Street, Suite 120, McLean, VA 22101, USA

* Corresponding author. 724 West Main Street, Suite 160, Lewisville, TX 75067.

E-mail address: anilnanda@yahoo.com

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COPD shares some features of asthma, and these conditions can overlap (asthma-COPD overlap, or ACO). Asthma can be allergic, nonallergic, or both. Nonpharmacologic therapies for asthma include patient education on inhaler technique and asthma action plan. Pharmacologic therapies include inhaled corticosteroids (ICS), inhaled corticosteroid-long-acting β -agonist combinations (ICS-LABA), leukotriene antagonists, long-acting muscarinic antagonists (LAMA), and short-acting β -agonists, as well as several biologics. Special populations include pregnant adults with asthma, patients with exercise-induced asthma/bronchoconstriction, older adults with asthma, and patients with occupational asthma.

PATHOPHYSIOLOGY OF ASTHMA

Airway inflammation is a hallmark of asthma, with eosinophils, mast cells, and most type 2 helper T lymphocytes (Th2, or T2, cells) involved.³ The specific cells involved in mild, moderate, or severe asthma can be variable, including T2 cells, type 1 helper lymphocytes (Th1, or T1 cells), eosinophils, and neutrophils.³ Cytokines associated with severe asthma include interleukin-17 (IL-17), IL-12, and IL-23.² Inflammatory cytokines associated with a Th2 response include IL-3, IL-4, IL-5, IL-13, and granulocyte-macrophage colony stimulating factor.³ A mixed pattern may predominate also, depending on exacerbating factors or severity.^{2,3}

Structural changes in the airway include mucous hypersecretion and an increase in the number of goblet cells and secretory glands.³ There may be evidence of epithelial damage, subepithelial fibrosis, and increased airway smooth muscle.³

DIAGNOSIS OF ASTHMA

The diagnosis of asthma is clinical and relies heavily on the history and physical examination, yet judicious use of diagnostic testing can assist in the diagnosis. Symptoms of asthma include cough, wheezing, and shortness of breath.⁴ Physical examination may display wheezing, hyperinflation, prolonged expiratory time, and increased labor of breathing.^{3,5} In severe exacerbations, cyanosis and use of accessory muscles of respiration may be evident.² However, some patients with severe asthma at baseline may not show the typical acute symptoms. For example, in patients with cough-predominant asthma, there may just be an inhalational cough. Atypical asthma presentations may lead to a misdiagnosis. Symptoms can be triggered by exercise, cold air, inhaled allergens, irritants, or stresses.³ However, examination is usually normal, because patients are often in between exacerbations.⁵ Imaging, including chest radiography, in asthma is usually normal, but bronchial thickening can occasionally be noted. Another test is allergy skin prick testing or measurement of specific immunoglobulin E (IgE) to determine if there is allergic asthma.⁶

In terms of diagnostic testing, spirometry is a PFT that measures the volume (amount) and flow (speed) of air that can be exhaled and inhaled and which can be done in the office setting.⁶ The forced expiratory volume in the first second of exhalation (FEV₁) is measured and is also compared with the forced vital capacity (FVC), the complete volume of air that can be exhaled in a forced attempt.⁶ A reduced FEV₁/FVC ratio (<0.75) demonstrates airflow obstruction.⁷ FEV₁ is often variable and coincides with a deterioration of improvement in symptoms.⁷ The predicted FEV₁ is calculated based on a variety of factors, including age, gender, weight, and ethnicity. There is usually a bronchodilator response to asthma with a 12% or greater than 200-mL increase of baseline FEV₁ about 10 to 15 minutes following administration of a short-acting β -agonist.⁶ However, some patients with a baseline FEV₁ of higher than 80%

may have a clinically significant bronchodilator response.⁷ Peak flow meters are less accurate than spirometers in the diagnosis of asthma.⁶

Measuring airway, or bronchial, hyperresponsiveness can also aid in the diagnosis of asthma.⁸ Traditionally, methacholine challenge has been used.⁸ Methacholine directly stimulates the constriction of airway smooth muscle, resulting in a discernible change in spirometry.⁸ Progressively increasing concentrations of methacholine are inhaled, and FEV₁ is serially measured.⁸ The concentration of methacholine that induces a decrease in FEV₁ of 20% is called the provocative dose, or PC₂₀.⁶ Typically, a PC₂₀ <1 mg/mL is moderate-severe bronchial hyperresponsiveness; a value between 1 and 4 mg/mL is mild bronchial hyperresponsiveness, and a value between 4 and 16 mg/mL is borderline responsiveness.⁹ A value greater than 16 mg/mL demonstrates normal bronchial hyperresponsiveness, essentially ruling out asthma.² However, the presence of bronchial (airway) hyperresponsiveness does not definitively diagnose asthma. For example, some patients with allergic rhinitis may have airway hyperresponsiveness during specific pollen seasons.¹⁰

Exhaled nitric oxide can also be used as a measure of eosinophilic airway inflammation. This method is less invasive than other methods of quantifying airway eosinophil levels and can be done in the office.⁶ Elevated FeNO levels (for example, >50 parts per billion) may predict an improved clinical response to ICS therapy.⁷

DIFFERENTIAL DIAGNOSIS OF ASTHMA AND ASSOCIATED COMORBIDITIES

The differential diagnosis of asthma is vast (Box 1). Conditions affecting multiple organ systems can present with symptoms similar to asthma. There are also multiple comorbid conditions associated with asthma. Upper respiratory tract conditions include vocal cord dysfunction, rhinitis and sinusitis, and OSA.² GERD is also associated with asthma. Other conditions in the differential diagnosis of asthma include congestive heart failure, pulmonary hypertension, and chronic thromboembolic pulmonary disease. Chest radiograph, computed tomography (CT) chest scan, and echocardiography can narrow down the diagnosis between these cardiovascular conditions. Foreign body airway obstruction and medication-related cough (such as

Box 1

Differential diagnosis of asthma

Vocal cord dysfunction

Rhinitis and sinusitis

OSA

Congestive heart failure

Pulmonary hypertension

Thromboembolic pulmonary disease

Foreign body airway obstruction

Medications (ACE inhibitors)

COPD

GERD

The above list depicts some conditions in the differential diagnosis of asthma, but is not intended to be an exhaustive list.

angiotensin-converting enzyme inhibitors [ACE inhibitors]) are also in the differential.⁷ COPD and ACO are discussed in subsequent sections of this article.

Vocal cord dysfunction is a “paradoxic movement of the vocal cords.”¹¹ Prevalence may be as high as 50% in severe asthma patients.¹¹ If a patient is not responding to typical asthma therapies, including ICSs, or symptoms appear to be more severe than spirometry indicates, vocal cord dysfunction should be considered. There is adduction of vocal cords, resulting in airflow limitation.¹¹ Potential triggers of vocal cord dysfunction attacks include exercise and anxiety. Symptoms include hoarseness, throat tightness, cough, dyspnea, and wheezing.¹¹ Diagnosis is made by laryngoscopy during exacerbations.¹¹ On spirometry, truncation of the inspiratory loop can occur.¹¹ Treatment is with speech therapy with specific breathing exercises. Similar to vocal cord dysfunction, exercise-induced laryngeal obstruction occurs when there is swelling of the aryepiglottic folds at the peak of exercise, with prompt resolution following exercise completion.¹¹

GERD is more common in patients with asthma, with prevalence rates as high as 74%.¹¹ GERD can present with chronic cough, as can asthma.¹² Of note, many patients may not have the “typical” symptoms of GERD, such as heartburn or dyspepsia. Treatment with lifestyle changes and daily proton pump inhibitors can be initiated.¹² The treatment of GERD has shown variable effects on asthma outcomes, but quality of life of asthma patients has been shown to be improved in some studies.¹¹

Rhinitis and sinusitis are common in patients with asthma. Both allergic and nonallergic rhinitis cause similar symptoms.¹³ Most patients with severe asthma are sensitized (have allergen-specific IgE to aeroallergens), and early onset of severe asthma is associated with allergic rhinitis and allergic conjunctivitis.¹¹ Patients with allergic rhinitis have worse asthma control with increase in number of exacerbations and emergency room visits.¹⁴ Approximately 48% of patients with chronic rhinosinusitis with nasal polyps have asthma.¹⁵ Therapies for rhinitis and chronic sinusitis include nasal saline rinses, intranasal corticosteroids, intranasal antihistamines, leukotriene inhibitors, and in the case of allergic rhinitis, allergen immunotherapy. Sinus surgery can also be an option for rhinitis and sinusitis with or without nasal polyps.¹⁶ In fact, difficult-to-control asthma in patients with sinusitis with or without nasal polyps can be an indication for surgery.¹⁶ Studies involving biologic medications are ongoing.

A subset of chronic rhinosinusitis patients with nasal polyps has a condition called aspirin-exacerbated respiratory disease.¹⁷ Classically, it is a triad of asthma, eosinophilic nasal polyps, and respiratory reactions caused by aspirin, nonsteroidal anti-inflammatory drugs (NSAID), and other cyclooxygenase 1 inhibitors.¹⁷ The respiratory reactions typically occur within 30 to 120 minutes of NSAID intake and induce asthma as well as rhinitis symptoms of rhinorrhea and nasal congestion.¹⁷ Aspirin desensitization, consisting of delivering gradual doses of aspirin and treating symptoms resulting from the provocative dose, can be performed until a concentration of 325 mg is reached.¹⁷ The patient then is maintained on high-dose aspirin therapy at 325 mg or 650 mg twice daily to maintain desensitization.¹⁷ Aspirin desensitization has been shown to decrease use of systemic corticosteroids and hospitalizations for asthma as well as improve sinusitis symptoms.¹³

OSA is frequently associated with asthma.¹⁸ OSA is characterized by episodes of apnea during sleep, and this is associated with upper airway obstruction and upper airway resistance.¹¹ Symptoms include daytime sedation and poor quality of sleep.¹¹ There is a higher frequency of OSA symptoms or polysomnography-diagnosed OSA in patients with asthma.¹⁸ Treatment of OSA (with continuous positive airway pressure or mechanical devices/surgery) improves asthma symptoms, bronchodilator use, and asthma-specific quality of life.¹⁸ One study showed that OSA risk may be associated

with neutrophilic asthma.¹⁸ Again, concomitant rhinitis should also be treated, because rhinitis can be a major contributor to upper airway resistance.¹⁹ Rhinitis, both allergic and nonallergic, may contribute to upper airway resistance syndrome.¹⁹ There appears to be a connection between upper and lower airways, involving a unified airway.¹⁹ Treatment of both the upper and the lower airways is paramount, rather than focusing on either one alone.¹⁹

Obesity is another comorbid condition associated with asthma. Obesity is correlated with increased asthma incidence, prevalence, and severity.²⁰ One study involving more than 10,000 adult asthma patients in the United States found a positive correlation between elevated body mass index and asthma exacerbations.²⁰ Another study showed that patients with increased abdominal visceral adiposity were associated with decreased asthma quality of life.²¹

Infections, including viral, bacterial, and fungal causes, are often comorbid conditions associated with asthma exacerbations.³ Allergic bronchopulmonary aspergillosis (ABPA) is a particular condition with diagnostic criteria, including asthma (or cystic fibrosis [CF]) with worsening lung function (FEV₁), *Aspergillus* mold sensitivity (positive specific IgE and IgG to *Aspergillus*), total serum IgE greater than 1000 ng/mL (416 IU/mL), and infiltrates on chest radiography.²² The main therapy consists of oral corticosteroids with antifungal therapies as an adjunct.²² Allergic fungal rhinosinusitis is a subcategory of rhinosinusitis with nasal polyps.²³ It is associated with mucus-containing eosinophils and allergy to fungus in the sinusitis.²³ Fungi involved are usually *Aspergillus*, *Bipolaris*, and *Alternaria* species.²³ Soft tissue densities are commonly found on CT scan of sinuses.²³ The main therapy for allergic fungal rhinosinusitis is functional endoscopic sinus surgery, and medical therapy with corticosteroids and antifungal agents can be adjuvant therapy.²³ One vasculitis in the differential diagnosis of asthma is eosinophilic granulomatosis with polyangiitis, typified by asthma, sinusitis, eosinophilia, pulmonary infiltrates, evidence of eosinophilic vasculitis, and peripheral neuropathy.¹¹

Depression is associated with asthma; however, the exact mechanisms are unknown.²⁴ Behavioral, affective, and cognitive dysfunction can influence medication use and inhaler technique.²⁴ One recent study revealed that depression was related to reduced bronchodilator use in asthma patients.²⁵ In the study, major depression was increased among patients with asthma (8.9%) compared with nonasthmatic patients (2.5%).²⁵ Controller medication underuse was linked to depression in asthma patients.²⁴ In 1 study of older adults, elevated depression scores correlated with decreased asthma control levels and reduced quality of life.²⁶

CF, a genetic disease owing to mutations in the CF transmembrane conductance regulator, is associated with respiratory exacerbations that can be similar to asthma.^{27,28} ABPA can also occur with CF, and its presentation may be indistinguishable from a CF exacerbation (shortness of breath, infiltrate on chest radiograph).^{27,28} Early recognition of both conditions is imperative, and ABPA should be considered in any CF patient with an exacerbation unresponsive to antibiotics.

TREATMENT OF ASTHMA

The main care components for asthma include assessment and monitoring, patient education, addressing environmental controls and comorbid conditions, and pharmaceutical therapy.²⁹ Assessment of asthma control is subdivided into impairment and risk.³⁰ The impairment component includes symptoms, nighttime awakenings, use of short-acting β -agonists, and pulmonary function.³⁰ Risk component includes exacerbations (such as requiring systemic corticosteroids), progressive loss of lung

function, and pharmaceutical side effects.³⁰ Tools for assessing asthma symptom control include the Asthma Control Questionnaire (ACQ) and Asthma Control Test (ACT), a 5-question test that is easy to access on the Internet and very practical to use at an office visit, taking less than a minute for a patient to complete.^{31–35} Scores on the ACQ from 0.0 to 0.75 indicate well-controlled asthma, and scores greater than 1.5 indicate poorly controlled asthma.^{31,32} Scores on the ACT of 20 to 25 indicate well-controlled asthma; 16 to 19 indicate not well-controlled asthma, and 5 to 15 indicate poorly controlled asthma.^{33–35} Patient education is paramount in the treatment of asthma because this is an outpatient disease, and patient adherence is increased with greater understanding of controller medication and exacerbation prevention. Patient adherence and inhaler technique are essential.²⁹ At every health care office visit, patient education should be emphasized. In addition, if there is evidence of allergic asthma, environmental controls, including reducing pet and dust mite exposure, may be implemented as well as treatment of allergic rhinitis.²⁹

PHARMACOLOGIC THERAPY FOR ASTHMA

Asthma severity can be further divided into intermittent and persistent, and these severities (including uncontrolled, partially controlled, and controlled) correspond with various steps of therapy (Table 1).^{29,30} Persistent asthma can be subdivided into mild, moderate, and severe and is treated with controller medications.^{29,30} Controller medications include ICSs, leukotriene inhibitors, combination ICS/LABA, LAMA, methylxanthines, cromolyn, and biologic medications.^{29,36} Allergen immunotherapy is also an option.³⁶ Reliever medications are rapid acting and include short-acting β_2 -agonists, such as albuterol and levalbuterol, as well as muscarinic cholinergic antagonists (anticholinergics), such as ipratropium bromide.²⁹

ICSs are the foundation of therapy for asthma-improving condition-related outcomes associated with both impairment and risks.^{29,36} The mechanisms of their

Table 1 Asthma severity				
Impairment	Intermittent	Mild Persistent	Moderate Persistent	Severe Persistent
Symptoms	≤2 d/wk	>2 d/wk	Daily	Multiple times per day
Night-time Awakenings	≤2/mo	3–4/mo	>1/wk	Daily
Short-acting inhaler use (β-agonist)	≤2 d/wk	>2 d/wk	Daily	Multiple times per day
Lung function	FEV ₁ >80% predicted	FEV ₁ >80% predicted	FEV ₁ >60% but <80%	FEV ₁ <60%
Exacerbations (requiring oral corticosteroids)	0–1/y	≥2/y	≥2/y	≥2/y
	Step 1	Step 2	Step 3 and/or 4	Step 5 and/or 6

Adapted from Durrani SR, Busse WW. Management of Asthma in Adolescents and Adults. In: Adkinson NF, Bochner BS, Burks AW, et al., editors. Middleton’s allergy principles and practice, 8th edition. Philadelphia: Saunders; 2014; and National Asthma Education and Prevention Program. Expert Panel Report 3 (EPR-3): Guidelines for the diagnosis and management of asthma-Summary Report 2007. J Allergy Clin Immunol 2007;120(5 Suppl):s94-s138; with permission.

actions include inhibition of inflammatory cell activation and migration.²⁹ Side effects are much lower than systemic corticosteroids, the long-term use of which is associated with the development of numerous conditions, including diabetes, osteoporosis, and decreased immunity. Low-dose inhaled steroids are recommended as first-line therapy for asthma.³⁶ Medium and higher doses of ICSs are also used.³⁶ Examples of low-dose inhaled daily corticosteroid therapies include fluticasone propionate 100 to 250 µg, budesonide 200 to 400 µg, and mometasone 110 to 220 µg.⁷ Medium-dose therapies include fluticasone propionate 250 to 500 µg, budesonide 400 to 800 µg, and mometasone 220 to 440 µg.⁷ Higher-dose therapies include fluticasone propionate 500 to 1000 µg, budesonide greater than 800 µg, and mometasone greater than 440 µg.⁷

The leukotriene pathway of inflammation involves the cysteinyl leukotrienes, and these are potent inflammatory lipid mediators.³⁷ Leukotriene receptor antagonists include montelukast and zafirlukast, and zileuton is in a similar medication class, because it modifies the 5-lipoxygenase pathway.²⁹ These medications are not as effective as ICS medications, but can be added on to inhaled steroid therapy.³⁶ They are less effective than combination ICS/LABA therapies.³⁶ Side effects in adults are minimal.³⁶

Combination ICS/LABA therapies are effective and are the preferred agents in adults whose asthma is not well controlled on low-dose ICS therapy.³⁶ The black-box warning of increased mortality in asthma patients taking LABA therapy, subsequently transferred to ICS/LABA therapy, was removed by the Food and Drug Administration owing to multiple safety trials.³⁸

LAMA, or anticholinergics, provide additional bronchodilation.^{39,40} LAMA medications, such as tiotropium, when added to ICS/LABA therapy, have been shown to reduce asthma exacerbations, and when added to ICS monotherapy, have improved asthma symptoms and lung function.^{40,41}

Methylxanthines, such as theophylline, provide bronchodilation with some anti-inflammation.³⁶ However, because of a narrow therapeutic window and common adverse events, such as nausea, vomiting, diarrhea, cardiac arrhythmias, and seizures, use of these medications should be for patients who cannot tolerate other therapies or who are still symptomatic despite other therapies.³⁶ Mast cell release inhibitors include cromolyn sodium, and these are safe; however, ICSs have better efficacy.²⁹ Long-term macrolide therapy has been proposed for severe asthma, but there has been inadequate evidence.⁴² In bronchial thermoplasty, radiofrequency pulses are used to treat the airway smooth muscle in patients with severe asthma; however, it is still unclear which patients should be selected for this procedure.^{36,42}

There is a prominent role of allergy in asthma, and patients with persistent asthma should be evaluated for contributing allergies. For allergic asthma in patients who are sensitized to inhaled allergens (aeroallergens), allergen immunotherapy has been shown to reduce asthma symptoms and the use of asthma medications.^{7,43} Airway hyperresponsiveness has also been improved.⁴³ Both subcutaneous and sublingual allergen immunotherapy have been shown to benefit asthma.^{42,44} The treatment of the upper airway, including rhinitis and chronic sinusitis, with medical therapies, such as intranasal corticosteroids, and if indicated, allergen immunotherapy, is also of paramount importance. In addition, comorbid conditions, such as GERD and sinusitis, must be considered and treated, especially in patients with poorly controlled asthma.

The newest agents for asthma are the biologic therapies. These agents are usually reserved for moderate to severe asthma patients. Currently approved biologics

for asthma involve anti-IgE, anti-IL-5, and anti-IL-4/anti-IL-13 antibodies. Omalizumab is a monoclonal antibody that attaches to free IgE and prevents activation of cells involved in the allergic inflammatory response, such as mast cells and basophils.⁴² Criteria for treating patients with omalizumab include positive IgE (skin test or serum-specific IgE) to an aeroallergen and elevated IgE levels (allergic asthma).⁴² Omalizumab, a subcutaneous injection, has been shown to reduce severe exacerbations and hospitalizations owing to asthma as well as reduce the dose of ICSs.⁴² Mepolizumab is a monoclonal antibody against IL-5, which reduces the number of eosinophils in both blood and sputum.⁴⁵ Mepolizumab, a subcutaneous injection, has been shown to reduce emergency room visits and hospitalizations owing to asthma.⁴⁵ Reslizumab, an intravenous agent, is also a monoclonal antibody to IL-5 and has also been shown to reduce asthma exacerbations.⁴⁶ Benralizumab, a subcutaneous injection, is a monoclonal antibody that attaches to the alpha-subunit of the IL-5 receptor, inducing a natural killer cell and antibody-mediated depletion of eosinophils.⁴⁷ It has also been shown to reduce oral glucocorticoid doses in patients with severe asthma as well as lower asthma exacerbation rates.⁴⁷ The most recent biologic approved for asthma is dupilumab, which had been previously approved for the treatment of atopic dermatitis. Dupilumab, a subcutaneous injection, is an anti-IL-4 receptor alpha-subunit monoclonal antibody that blocks both IL-4 and IL-13 signaling.⁴⁸ IL-4 and IL-13 are involved in Th2 inflammation.⁴⁸ Dupilumab has been shown to decrease severe asthma exacerbations and improved asthma control and lung function.⁴⁸ Dupilumab also has been shown to reduce oral corticosteroid use in severe asthma.⁴⁹

The overall treatment of asthma using the above therapies is indicated in **Table 2**.^{29,30} **Tables 1** and **2**, using step therapies, are only guides, and individualized patient assessment and therapy are essential. In addition, therapy can be “stepped up” or “stepped down” depending on the clinical situation.

Table 2 Treatment of asthma					
	Intermittent	Mild Persistent	Moderate Persistent	Moderate Persistent	Severe Persistent
Step	Step 1	Step 2	Step 3	Step 4	Step 5 and Step 6
Treatment	Short-acting β-agonist as needed	Low-dose ICS	Medium-dose ICS Or Low-dose ICS-LABA	Medium-dose ICS-LABA	High-dose ICS-LABA LAMA May also consider biologic therapies
Alternative		Leukotriene antagonist	Low-dose ICS and leukotriene antagonist	Medium-dose ICS and leukotriene antagonist LAMA may be added	Oral prednisone may need to be added

Allergen immunotherapy can also be considered for allergic asthma.
Adapted from Durrani SR, Busse WW. Management of Asthma in Adolescents and Adults. In: Adkinson NF, Bochner BS, Burks AW, et al., editors. Middleton’s allergy principles and practice, 8th edition. Philadelphia: Saunders; 2014; and National Asthma Education and Prevention Program. Expert Panel Report 3 (EPR-3): Guidelines for the diagnosis and management of asthma-Summary Report 2007. J Allergy Clin Immunol 2007;120(5 Suppl):s94-s138; with permission.

TREATMENT OF ACUTE ASTHMA EXACERBATIONS

Usually, with regular therapy and education, asthma exacerbations requiring emergency department visits or hospitalization can be avoided; however, 12 million people in the United States per year suffer from acute asthma exacerbations, with approximately 3 million hospitalized.¹ Severe asthma signs include tachypnea, tachycardia, use of accessory muscles of respiration, diaphoresis, wheezing (although lack of airflow or diminished breath sounds may also indicate severe asthma), and difficulty in lying down.¹ However, in severe, chronic asthmatics, these signs may not be seen. Bradycardia can be a sign of imminent respiratory failure.¹ Risk factors for fatal asthma or near-fatal asthma include multiple hospitalizations or emergency room visits, intensive care unit admission or intubation/mechanical ventilation, excessive short-acting β -agonist use, and allergy to the mold, *Alternaria*.¹ Spirometry can be used, measuring FEV₁ as well as peak flow, to assess change from baseline.¹ Laboratory evaluation or chest radiographs are usually not required, unless there are comorbid conditions or the diagnosis is uncertain.¹ Arterial blood gases can be considered in acutely ill patients, including patients with oxygen saturation of less than 92% on room air.¹ Arterial blood gases can give information on respiratory status, impending respiratory fatigue, and respiratory failure.¹

Treatment consists of short-acting β -agonists, such as albuterol, either by metered dose inhaler or by nebulized therapy, with continued treatments until the patient has become stable.¹ Ipratropium bromide, an anticholinergic, can also be added.¹ Corticosteroids are also vital concomitant therapies. In the outpatient setting, ICSs can be considered for mild asthma exacerbations, usually quadrupling the recommended dose of the ICS.¹ Short courses of oral corticosteroids can also be effective, with no tapering required if less than 3 weeks of treatment.¹ In the acute setting, such as the emergency room, systemic corticosteroids should be used (either oral, intravenous, or intramuscular).¹ Oral steroids are recommended after emergency room discharge.¹

Failure to respond to the above therapies requires hospitalization.¹ Noninvasive positive pressure ventilation can be attempted in patients at an increased rate of respiratory failure; however, intubation should not be delayed once it is thought to be clinically necessary.¹ High ventilator pressures should be avoided to avoid the risk of barotrauma.¹ Upon discharge, patient education should be emphasized with appropriate follow-up with an asthma specialist, such as an allergist/immunologist.¹

ASTHMA IN PREGNANCY

Approximately 8% of pregnant women report asthma, which incurs higher risks of pregnancy complications, including preeclampsia and preterm birth.⁵⁰ Improved asthma control can lead to improved pregnancy outcomes.⁵⁰ Asthma can worsen, improve, or remain the same during pregnancy.⁵⁰ Most patients have a diagnosis of asthma before pregnancy, but new onset pulmonary symptoms during pregnancy should be evaluated.⁵⁰ Spirometry and allergy testing (through use of specific IgE, and not allergy skin testing) can be used to evaluate symptoms, if necessary, but methacholine testing is contraindicated in pregnant patients because of lack of safety data.⁵⁰

Comorbid conditions should be treated, including rhinitis (both allergic and nonallergic), sinusitis, and GERD.⁵⁰ Pregnant patients with well-controlled asthma should continue the medications.⁵⁰ Rapid-acting therapy includes short-acting β -agonists, including albuterol.⁵⁰ Among controller medications, ICSs are the most effective

medications.⁵⁰ Budesonide is a pregnancy medication class category B corticosteroid.⁵⁰ It is recommended for women on controller medication to be seen on a monthly basis.⁵⁰ Most data on adverse effects of medications for asthma are from observational studies, but most data are reassuring.⁵⁰

Asthma exacerbations should be treated with short-acting β -agonists, anticholinergic medications, and systemic corticosteroids.⁵⁰ Fetal assessment is contingent on pregnancy stage.⁵⁰ Asthma medications should be continued during labor and delivery.⁵⁰

ASTHMA AND EXERCISE-INDUCED BRONCHOCONSTRICTION IN ADULTS

Exercise-induced bronchoconstriction (EIB) refers to the momentary narrowing of the airways after exercise.⁵¹ EIB occurs among adults who may not even have asthma symptoms otherwise.⁵¹ Asthma is more common among endurance athletes, such as winter-sports athletes and swimmers.⁵¹ The mechanism may involve airway dehydration during increased ventilation on exercise, and this increases osmolarity of fluid lining the airways.⁵¹ The resulting release of mediators causes airway bronchoconstriction.⁵¹

EIB usually occurs within 15 minutes after 5 to 8 minutes of intensive aerobic training and usually resolves within 60 minutes.⁵² Symptoms alone are not enough for diagnosis.⁵¹ Objective testing includes exercise challenge, eucapnic voluntary hyperpnea (EVH), and mannitol challenges.⁵³ In adult recreational or elite athletes suspected of having EIB who have normal lung function and no clinical history of asthma, an indirect, ungraded challenge (exercise or EVH) can be performed.^{53,54} As an example, during an exercise challenge, a 10% or greater decrease in FEV₁ compared with pre-exercise baseline at any 2 consecutive time points during challenge is diagnostic of EIB.⁵³ Vocal cord dysfunction, discussed previously, is important to consider in the differential.⁵¹

Nonpharmacologic therapies include addressing environment (such as improving ventilation in indoor pools), using face masks to decrease cold air exposure, and using a preexercise warmup.⁵¹ Treating underlying asthma in athletes, with therapies noted previously (such as ICSs), is important. Pharmacologic therapies for EIB include the use of short-acting β -agonists 5 to 10 minutes before exercise, but overuse can cause tolerance.⁵¹ Leukotriene antagonists also decrease EIB and can be considered as well as cromolyn products as alternative therapies.⁵¹ Exercise challenge can be difficult to perform in the outpatient setting, so a trial of a β -agonist before exercise is a prudent first step. If there is no improvement in symptoms, conditions such as uncontrolled asthma and vocal cord dysfunction can be further considered.

ASTHMA IN OLDER ADULTS

It is estimated that there is an approximate 7.8% prevalence of asthma among people 65 to 74 years old and a 6% prevalence in people 75 years and older.⁵⁵ Diagnosing asthma in adults can be more difficult because of multiple comorbid conditions, and management can be more challenging because of medication side effects and diminished cognition.⁵⁵ Again, asthma education is a critical component; however, there are some unique circumstances regarding older adults.⁵⁵ Arthritis, affecting many older adults, can lead to difficulty in using inhalers, especially metered dose inhalers.⁵⁵ In addition, polypharmacy is common in the older adult population.⁵⁵ Depression also is common and should be addressed.⁵⁵

ASTHMA CHRONIC OBSTRUCTIVE PULMONARY DISEASE OVERLAP

Like asthma, COPD is an inflammatory condition of the airway, but is generally associated with tobacco smoking and older patients.⁵⁶ Patients have airflow limitation, and the condition is usually progressive.⁵⁶ Forms of COPD include emphysema and chronic bronchitis.⁵⁶ COPD has been considered a neutrophilic, rather than eosinophilic inflammatory disease; however, there is evidence that both COPD and asthma can have eosinophilic and neutrophilic pathologies.⁵⁶ ACO refers to a combination of asthma and COPD features.⁵⁶ Bronchial hyperresponsiveness, thought to be a trademark of asthma, occurs in COPD patients also, and many asthma patients have a significant smoking history also.⁵⁶ Treatment of ACO consists of ICSs, LAMAs, and long-acting β -agonists, which are currently used in the therapy for both asthma and COPD.⁵⁶ However, there is still no firm consensus for either the diagnosis or the exact treatment of ACO.

OCCUPATIONAL ASTHMA

Occupational asthma occurs when an agent at a workplace causes the asthma.⁵⁷ Atopy (presence of IgE antibodies) to inhaled allergens is associated with the development of asthma to high-molecular-weight agents.⁵⁷ Some examples of more common high-molecular-weight agents include flour (wheat, rye with bakers), latex (gloves in health care workers), and animal proteins (mice, rat dander in laboratory workers).⁵⁷ Low-molecular-weight agents include isocyanates, metals, acid anhydrides, acrylates, and wood dusts and are common in the manufacturing industries.⁵⁷ In addition to the history and physical examination, diagnosis includes specific IgE testing, bronchial responsiveness challenge (such as methacholine challenge), and laboratory challenges with a suspected occupational agent.⁵⁷ Avoidance of the causative agent is the ideal treatment.⁵⁷

SUMMARY

Asthma is a relatively common condition and can be frequently underdiagnosed or misdiagnosed. Today's internist will encounter patients with this condition frequently.

Asthma is also associated with multiple comorbid conditions, which may exacerbate asthma if not also controlled. New therapies include biologics, and there are multiple new modalities of treatment in the pipeline. Referral to an asthma specialist, such as an allergist/immunologist, should be considered if the diagnosis is in doubt, if initial treatment is ineffective, or if there are multiple comorbidities. Individualized and precision therapy for each patient is essential.

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